REMARKS

Claims 22-58 presently appear in this case. No claims have been allowed. The official action of October 4, 2007, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method for treating a viral infection by the administration of interferon via oromucosal contact. The unit dose is a high dose which is greater than about 0.28×10^6 IU of interferon per kg body weight of the patient, preferably greater than 30×10^6 IU of interferon. In a preferred embodiment, the unit dose is administered via oromucosal contact intranasally. The administration via oromucosal contact is preferably in a manner that does not involve direct action of the interferon on virally infected cells and by which the biologically active interferon does not enter the blood stream. In a further preferred embodiment, the viral infection is other than a rhinoviral infection. In another preferred embodiment, the viral infection may be a rhinoviral infection , but the administration via oromucosal contact is by means of a single unit dose that is not a plurality of smaller amounts administered over a period of time sufficient to elicit a response equivalent to that of a single unit dose.

Claims 22-58 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The examiner states that claims 36, 52 and 58 recite the limitation "an effective amount of grater than 0.28 x 10^6 IU of interferon per kg body weight" or "an amount of greater than 30 x 10^6 IU of interferon." The examiner states that the claims also recite the limitation, "said amount being in excess of an amount of the same interferon which induces a pathological response when parenterally administered." The examiner considers this to be redundant and indefinite. This part of the rejection is respectfully traversed.

In order to avoid any ambiguity in the claims, all of the independent claims have now been amended to delete the term "said amount being in excess of an amount of the same interferon which induces a pathological response when parenterally administered." Thus, this part of the rejection has now been obviated.

The examiner states that the claimed doses are indefinite because it is not clear if the claimed dose limitations are referring to a total daily dose or a per administration dose. The examiner states that dependent claims recite administration in both a single administration as well as administration in multiple doses and, accordingly, the doses recited in the claims could reasonably be

interpreted as single administration doses as well as a total daily dose. This part of the rejection is respectfully traversed.

All of the independent claims have now been amended to specify that the effective amount stated in the claims is "a unit dose." Attached hereto is a declaration of the present inventor, Dr. Michael Tovey, relating to this issue. In this declaration, Dr. Tovey explains what is meant by the term "a single dose of interferon." For the purpose of this explanation, one of ordinary skill in the art would understand that "single dose" and "unit dose" are the same thing. Dr. Tovey explains that interferons work by binding to specific high affinity receptors on target cells and that a single administration of optimum dosage will saturate those receptors or at least bind an appropriate number of such receptors. Over a period of time, interferon bearing receptors are down-regulated and new binding sites become available for binding to additional interferon. Thus, a "single dose" (or a "unit dose") does not mean a daily dose, but the dose of each administration for optimum effect of that single administration. This is then repeated every several hours as needed. The declaration than cites references to this effect and concludes that when the present application refers to "a single dose or multiple and continuous administration of

smaller doses to have the same cumulative effect as a single dose" one is referring to multiple or continuous administration over the period of optimum activity of a single dose, i.e., all fairly quickly so as to achieve the optimum saturation of receptors equivalent to that of a single dose. A claim directed to multiple administrations of smaller doses would not be anticipated by a reference disclosing administration of a smaller dose once every several hours. Note that the term "unit dosage form" is supported on page 7, lines 11-12, of the present specification.

Accordingly, claim36 now provides that the method comprises administering "a unit dose comprising an effective amount of greater than 0.28×10^6 IU of interferon per kg body weight of the patient." Claim 38 further specifies that the unit dose of interferon is administered in a single unit dose as opposed to a plurality of smaller amounts administered over a period time sufficient to elicit a response equivalent to that of a single unit dose and claim 39 specifies that the unit dose of interferon is delivered in a plurality of smaller amounts over a period of time sufficient to elicit a response equivalent to that of a single unit dose. This language is consistent with the explanation in the Tovey declaration and with what a person of ordinary skill in the art would understand to be the meaning of the disclosure in the present

specification about preferred effective amounts, all for the reasons explained by Dr. Tovey. Accordingly, particularly as amended, the present claims are no longer even arguably indefinite. Reconsideration and withdrawal of this part of the rejection is also respectfully urged.

Claims 36 and 38-51 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite because claim 36 recites the broad recitation "oromucosal contact" and the claim also recites "intranasally," which is the narrowest statement of the range/limitation. The examiner considers this to be indefinite. The examiner again also refers to the specific dosage specified and the "amount greater than an amount that induces a pathological response" language.

Claim 36 has now been amended so that there are not now two administration limitations, but only a single one. The "wherein the interferon is administered intranasally" phrase has been deleted from the end of the claim and the oromucosal contact language has been changed to read "via oromucosal contact intranasally." Accordingly, this is now a single recitation and does not suffer from the ambiguity noted by the examiner. As indicated above, the language about being in excess of a pathological amount has now been deleted, thus, obviating this part of the rejection.

Accordingly, reconsideration and withdrawal of the entire 35 U.S.C. 112, second paragraph, rejection is respectfully urged.

Claims 22-58 have been rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for treating a rhinoviral infection with recombinant interferon-α_2 does not reasonably provide enablement for treating any and all viral infections via oromucosal administration of any interferon. The examiner states that this is an enablement rejection. The examiner concedes that the relative skill of those in the art is high. The examiner considers the nature of the art to be unpredictable. The examiner states that it is not clear how an infection could be treated if interferon does not act on the viral cells and does not enter the blood stream. Further, the examiner refers to Hayden (1988) for showing that systemic infection was not affected by intranasal interferon treatment. Thus, the examiner considers it unpredictable whether a high dose of oromucosally administered interferon, which does not directly affect viral cells and does not enter the blood stream as a biologically active agent, will have any beneficial effect in treating any and all viral infections, especially systemic viral infections. This rejection is respectfully traversed.

It is respectfully submitted that Smith, the two Hayden references and Santus do not cause one of ordinary skill in the art to doubt the disclosed utility of the present invention relating to all types of viral infections. Smith and both Hayden references treat the virus directly with interferon, not indirectly as in the present invention. The direct treatment of such an acute virus, even if the virus is in the nose, would not be expected to cast doubt on claims that explicitly exclude direct contact of the interferon with the virus.

Santus is inapplicable because, as the examiner recognizes, Santus has nothing to do with interferon. It has already been shown that interferon can be administered by oromucosal administration and therefore Santus could not be applicable to interferon.

The present applicants have many papers in prestigious journals concerning the present invention. Attached hereto are the following papers:

Tovey, MG et al., "Oromucosual Interferon Therapy: Marked Antiviral and Antitumor Activity", *J. Interferon Cytokine Res.*, 19:145-155 (1999). This paper shows that oromucosally administered interferon exerted a marked antiviral activity in mice challenged systemically with a

lethal dose of encephalomyocarditis virus (EMCV), vesicular stomatitis virus (VSV), or varicella zoster virus (VZV).

Eid et al., "Oromucosal Interferon Therapy: Pharmacokinetics and Pharmacodynamics", *J. Interferon Cytokine Res.*, 19:157-169 (1999). This paper shows that oromucosal interferon treatment activated gene transcription locally in the lymphoid tissue of the oropharyngeal cavity and caused a marked systemic antiviral activity. It discloses that the present invention may work because it involves either production of a soluble factor or activation of a specific cell population that enters the circulation to mediate the elimination of virus-infected or neoplastic cells.

Schellekens et al., "Oromucosal Interferon Therapy: Relationship Between Antiviral Activity and Viral Load", *J. Interferon Cytokine Res.*, 21:575-581 (2001). This paper also shows the effect of oromucosal IFN therapy in protecting mice challenged with a lethal dose of EMCV and that the invention may be most effective in chronic viral infections.

Also attached hereto is Tovey, "Oromucosal Cytokine Therapy: Mechanism(s) of Action", *Taehn Kan Hakhoe Chi.*, 8:125-131 (2002). This article reviews all the work that has been done with respect to the invention and summarizes at page 129 in the last paragraph before section VIII:

> In summary, oromucosal administered IFN α binds to high affinity receptors on the

> surface of lymphoid cells of the oral cavity leading to activation of IFN responsive genes resulting in both the activation of specific populations of immuno-competent cells which migrate to the site of virus replication … and the production of chemokines which enter the peripheral circulation and redirect lymphocyte trafficking to eliminate virus infected cells ….

In the sentence bridging the columns of page 130, this paper states:

> Thus, oromucosal IFN therapy would be expected to be most effective in chronic disease such as chronic viral hepatitis, as an alternative to parenterally administered interferons which are clinically effective but poorly tolerated.

The last sentence of the paper states:

> Furthermore, the availability of a well tolerated form of IFN therapy will also allow the Type I IFNs to be used for the treatment of diseases such as upper respiratory tract virus infections, for which parenteral IFN therapy is currently precluded due to unacceptable toxicity

Accordingly, the statements made in the present specification are not incredible and it would not take undue experimentation to use this invention as broadly as is disclosed. While the invention may work better with some viruses than others, there is no reason to believe that there will be no effect on any virus when the interferon is administered in the manner presently claimed.

As to the examiner's comments that there is no data relating to treatment of any previously established viral conditions, see the papers the abstracts of which are attached hereto and discussed above. As to the doses, the present specification indicates that the higher the dose the better, and that the problems of interferon toxicity involved with parenteral administration of interferon do not appear. Thus, there is nothing except cost that would prevent the use of very high dosages of interferon. There is no reason to believe that the higher the dose the greater the effect no matter what the infection is. Accordingly, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 36, 39-43, 46-47 and 49-51 have been rejected under 35 U.S.C. 102(b), as being anticipated by Hayden (1984). The examiner states that Hayden teaches intranasal administration of 9×10^6 HuIFN-2α three times per day for five days to patients having rhinoviral infections. Thus, the examiner states that total daily dose is equivalent to 27×10^6 IU interferon, thus meeting the instantly claimed limitation when interpreted as being administration of a total daily dose of greater than 0.28×10^6 IU of interferon per kg body weight of the patient. This rejection is respectfully traversed.

As explained hereinabove, the claims have now been amended to specify that each unit dose is greater than 0.28 x

10^6 IU of interferon per kg body weight of the patient. Thus, this is not a total daily dose, but a total unit dose. The Tovey declaration explains how one of ordinary skill in the art would understand this terminology in the present specification. Administering interferon three times a day, i.e., eight hours apart, is not administration of smaller doses that are equal to the administration of a single unit dose of the specified amount. When administered many hours apart, these are individual, single unit doses. Accordingly, Hayden does not anticipate the present claims. Reconsideration and withdrawal of this rejection are respectfully urged.

Claims 23-27, 30-31, 33-35 and 38 have been rejected under 35 U.S.C. 103(a), as being unpatentable over Hayden (1984). The examiner states that the instant claims differ from Hayden in the dose of interferon being administered and that the total daily dose of Hayden is 27 x 10^6 IU interferon, whereas the instant claims recite administration of greater than 30 x 10^6 IU interferon. The examiner states that it would have been obvious to increase the total daily dose of 27 x 10^6 IU interferon to a total daily dose of 30 x 10^6 IU of interferon. This rejection is respectfully traversed.

As indicated above in the anticipation rejection, the dosage limitation of the present claims is directed each

unit dosage, i.e., each single dosage. Interferon administered eight hours apart is not one single unit dose, but three separate single unit doses of 9×10^6 IU each. Administration of 30×10^6 IU interferon would not be obvious from a disclosure of the administration of 9×10^6 IU interferon, particularly in view of the known side effects of high doses of interferon. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 22-35 and 37 have been rejected under 35 U.S.C. 103(a), as being unpatentable over Eby III. The examiner states that the instant claims recite methods for treating viral infection as comprising administering greater 30×10^6 IU interferon of an interferon via oromucosal contact. The examiner states that Eby discloses an example of interferon composition that can comprise 1-20 million IU and that if a 5 gram fructose based lozenge containing 20 million IU of interferon is administered twice, a total of 40 million IU interferon would be administered, thus meeting the limitation of greater than 30×10^6 IU as recited in claim 37. The examiner states that the skilled artisan would be motivated to adjust the administration amount in consideration of individual patient response. This rejection is respectfully traversed.

A similar rejection was made in this case in the official action of August 30, 2001. This rejection was withdrawn when applicant argued in the amendment of January 25, 2002, that Eby teaches the extremely wide dosage range of 1-20 million IU and that one would expect such a dosage range to cover only that which was active. In other words, one would expect a bell curve of activity with the optimum activity at about 10 million IU, but that one would not expect any activity below 1 million IU or greater than 20 million IU. Alternatively, one would assume that the side effects would be too great above 20 million IU. When an applicant inserts such a large range, those of ordinary skill in the art would assume that it includes everything that is active. Therefore, there would be no motivation for one of ordinary skill in the art to use even one IU more than 20 million IU. Based on this argument, the previous rejection was withdrawn. It is not understood why it is being resurrected six years later in the same case. The 1-20 million IU range is not merely an example; interferon is merely an example among many other possible rhinoviral medications. However, the range is such a wide range that it cannot be considered to be an example, but would be considered by one ordinary skill in the art reading the application as being the total range of operability for interferon.

With respect to the examiner's comments about administering the lozenge twice, again the present claims specify that the dosage amount is a single unit dose. Administering the lozenge twice would be two doses and not a single unit dose. Thus, one of ordinary skill in the art would not consider any of the present claims to be obvious over Eby. Reconsideration and withdrawal of this rejection is therefore also respectfully urged.

Claims 36, 38-51 and 58 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Eby in view of Hayden (1983). The examiner states that Eby discloses a method of treating the common cold by administering medicaments to and into the oral tissues. The examiner states that Hayden teaches methods of administering interferon-α_2 by intranasal drops, either daily or in multiple treatments, i.e., four times per day for four days. The examiner states that frequent intranasal administration of human leukocyte-derived IFN was associated with a reduction in infection rates in volunteers challenged with rhinovirus. The examiner states that the presently claimed methods would have been *prima facie* obvious. The examiner states that where the general conditions of a claim are disclosed in the prior art it is not inventive to discover the optimum or workable ranges by routine administration. The examiner states that as Eby

generally discloses methods for treating rhinoviral infections via oromucosal contact the present invention is not inventive over Eby, particularly in view of Hayden's disclosure of intranasal administration. This rejection is respectfully traversed.

The examiner is misreading Eby where he states that Eby "does not teach intranasal administration in multiple doses." The examiner appears to ignore that Eby is not merely silent about intranasal administration in multiple doses. Eby explicitly says that the invention will not work if administered intranasally or if administered in multiple doses. This is an explicit teaching away from the present invention. How could it be merely a discovery of optimal or workable ranges by routine experimentation to do something that the reference says one must not do? In this regard the examiner's attention is invited (as it has been invited many times during the lengthy prosecution of this case) to column 5, lines 27-42, particularly where it states:

> From the observation that zinc … shorten common colds when applied to the oral cavity, this inventor now teaches that the reason all … interferons … fail, or produce limited results is because they are not applied to the lining of the mouth in a sustained and repeated fashion, rather they are applied to the more logical and more obvious treatment locus, the interior of the nose ….

Eby goes on to state in the following paragraph:

> This inventor teaches that all … interferons … must be administered to the roof of the mouth, the interior cheeks of the mouth, the tongue, the oromucosa, the oralpharyngeal mucosa and all other interior surfaces of the mouth and to the throat … to be effective."

The sentence bridging columns 5 and 6 of Eby states:

> This inventor teaches that the efficacious use of … interferons … is enhanced and optimized when said medicaments are not administered … by application to the nasal tissues directly …."

Clearly, Eby teaches away from the present invention as claimed in claim 36.

Hayden fulfills none of the deficiencies of Eby as one of ordinary skill in the art reading Hayden would have no reason to believe that Eby's explicit disclosure teaching away from nasal administration should be ignored. Furthermore, Hayden uses an extremely low dosage of interferon. Unit doses of 11×10^4 four times a day is four unit doses. The present claims do not read on total daily dose, but read on total unit dose.

Accordingly, as no combination of Eby and Hayden would make obvious the present claims, which administer the interferon in a way that Eby explicitly discloses may not be used. It would not have been *prima facie* obvious to one of ordinary skill in the art to disregard these disclosures of Eby and instead administer the highest dose of interferon

disclosed by Eby, which is orders of magnitude greater than that applied by Hayden, nasally and expect it to work. Reconsideration and withdrawal of this rejection are also respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By /rlb/
Roger L. Browdy
Registration No. 25,618

RLB:jmd
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\P\phaq\Tovey1A\Pto\2008-03-04AmdN.doc